Surg Endosc (2015) 29:3485–3490
DOI 10.1007/s00464-015-4098-9

Recurrence of biliary disease following non-operative management in elderly patients

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Received: 6 August 2014 / Accepted: 16 January 2015 / Published online: 12 February 2015

Abstract
Introduction The purpose of this study was to determine the proportion of symptomatic recurrence following initial non-operative management of gallstone disease in the elderly and to test possible predictors.
Methods This is a single institution retrospective chart review of patients 65 years and older with an initial hospital visit (V1) for symptomatic gallstone disease, over a 4-year period. Patients with initial "non-operative" management were defined as those without surgery at V1 and without elective surgery at visit 2 (V2). Baseline characteristics included age, sex, Charlson comorbidity index (CCI), diagnosis, and interventions (ERCP or cholecystostomy) at V1. Outcomes assessed over 1 year were as follows: recurrence (any ER/admission visit following V1), surgery, complications, and mortality. A survival analysis using a Cox proportional hazards model was performed to assess predictors of recurrence.
Results There were 195 patients initially treated non-operatively at V1. Mean age was 78.3 ± 7.8 years, 45.6 % were male, and the mean CCI was 2.1 ± 1.9. At V1, 54.4 % had a diagnosis of biliary colic or cholecystitis, while 45.6 % had a diagnosis of cholangitis, pancreatitis, or choledocholithiasis. 39.5 % underwent ERCP or cholecystostomy. Excluding 10 patients who died at V1, 31.3 % of patients had a recurrence over the study period. Among these, 43.5 % had emergency surgery, 34.8 % had complications, and 4.3 % died. Median time to first recurrence was 2 months (range 6 days–4.8 months). Intervention at V1 was associated with a lower probability of recurrence (HR 0.3, CI [0.14–0.65]).
Conclusion One-third of elderly patients will develop a recurrence following non-operative management of symptomatic biliary disease. These recurrences are associated with significant rates of emergency surgery and morbidity. Percutaneous or endoscopic therapies may decrease the risk of recurrence.

Keywords Cholecystectomy · Clinical papers/trials/research · ERCP (endoscopic retrograde cholangiopancreatography) · Gallstones · CBD (common bile duct) · Elderly

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Gallstone disease in the elderly is very common. It often presents as complicated disease, with atypical symptomatology [1], which can lead to diagnostic uncertainty and treatment delays. Although some studies have shown greater conversion and complication rates following laparoscopic cholecystectomy in this population [2–5], most suggest that, given an acceptable perioperative risk profile, elderly patients with symptomatic gallstone disease should be treated surgically [6–10].

Despite this, our group previously published a report indicating that a larger than expected number of elderly patients who presented to the emergency department with biliary disease did not undergo surgery [11], a finding

shared by others [12–15]. In our study, as age increased, the likelihood of undergoing surgery within the year following presentation decreased dramatically, from 87 % for those aged between 65–74 to 22 % in those 85 years and older [11]. The reason behind these observations may simply be surgeon reticence to operate on the very old [12, 13, 16], patient preference, or perhaps non-operative management in this population is completely justified based on comorbidities, or the presence of complicated disease [13, 17, 18]. What remains unclear is the impact of non-operative management on the patient and whether it is possible to predict which patients will recur following non-operative treatment.

The purposes of this study were as follows: (1) to describe the outcomes of non-operative management of gallstone disease in elderly patients, with the primary outcome being time to recurrence and the secondary outcomes being complications and mortality; (2) to identify predictors of recurrence.

Methods

This is a single institution retrospective chart review of patients 65 years and older who underwent non-operative management for symptomatic gallstone disease (biliary colic, cholelithiasis, cholecystitis, choledocholithiasis, pancreatitis, or cholangitis), at the time of their initial hospital visit (V1) for this condition, between April 1, 2004, and May 31, 2008. Exclusion criteria were as follows: (1) patients with asymptomatic or incidental gallstones, biliary malignancy, primary choledocholithiasis [common bile duct (CBD) stones found >1 year following cholecystectomy], or pancreatitis of any etiology other than biliary, (2) patients with emergency or elective surgery at V1, and (3) patients who died during V1. Hospital visits included elective surgery admissions as well as emergency department (ED) visits with or without subsequent urgent admission. Outpatient visits were not reviewed, as these data were not available in the hospital charts. Data were extracted up to 1 year following the initial visit for all patients. This study received ethics approval from the Jewish General Hospital, Montreal, Quebec, Canada.

Baseline characteristics

The following demographic characteristics at the initial visit were extracted from the chart: age, gender, and the Charlson comorbidity index (CCI). The CCI predicts the risk of death from comorbid disease using weighted scores for the following comorbidities: coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, chronic renal disease, cancer, metastases, and AIDS [19]. In this study, the CCI was based on all comorbidities recorded over all previous visits. Diagnoses were grouped as gallbladder disease (colic, cholecystitis) and CBD disease (choledocholithiasis, cholangitis, pancreatitis). Therapeutic interventions at V1, including the use of percutaneous cholecystostomy tube and endoscopic retrograde cholangiopancreatography (ERCP), were also collected.

Study outcomes over 1-year period

The primary outcome of the study was time to recurrence. Recurrence was defined as any visit to the ED (with or without admission) due to recurrence of the disease following non-operative management at V1. This excludes ED visits due to complications of disease (e.g., myocardial infarction following diagnosis of acute cholecystitis), complications of treatment of disease (e.g., Bleeding post-ERCP), as well as hospital visits for elective surgery.

Among patients with at least one recurrent visit, secondary study outcomes included the number of recurrent visits, emergency and elective surgery, use of cholecystostomy tubes or ERCP, complications during subsequent visits, and change in diagnosis group from initial visit to first recurrent visit (e.g., gallbladder disease at V1 and CBD disease at V2). Surgery was considered elective when it occurred following elective admission and urgent when it occurred following admission from the ED. Among patients with no recurrent visit, return visits for elective surgery were reported. Deaths occurring during the study period were also recorded for all patients.

Statistical analysis

Baseline characteristics at first visit were described for all patients and stratified by recurrence/no-recurrence. Study outcomes were also summarized for patients with and without recurrent visits. Proportions were calculated for categorical variables, and means ± standard deviations were used for continuous variables. A survival analysis using a Cox proportional hazards model was performed to assess the effect of the baseline characteristics on time to recurrence. Patients were deemed "censored" if no recurrence of the disease occurred by the end of the study period or if patients underwent elective surgery. Patients undergoing elective surgery were not considered to have had a hospital visit because of recurrence of the disease but rather because of planned surgery. Moreover, patients were censored at the time of surgery, since postsurgical recurrence, while possible, remains unlikely. Assumptions of proportionality of the model were tested and verified. A Kaplan–

Meier survival curve for time to recurrence of disease was also created. p values <0.05 were considered statistically significant. All analyses were conducted using SAS 9.2 (Cary, NC).

Results

Patient characteristics

Data from 397 patient charts were assessed, and 195 patients met the inclusion criteria (Fig. 1). In this study, there were 127 visits following V1 and 46 patients recurred. Table 1 summarizes the baseline demographics at V1 grouped by recurrence. The overall mean age of patients was 78.3 years and was comparable in both groups. The CCI was also found to be similar among groups. A higher proportion of males was found in the recurrence group, 58.7 versus 41.6 % in the non-recurrence group. At V1, the no recurrence group had a significantly higher rate of intervention in the form of ERCP or cholecystostomy tube (46.3 %) when compared to the recurrence group (17.4 %). A higher rate of gallbladder disease was noted in the recurrence group (69.6 %) when compared to CBD disease (30.4 %).

Results over study period

The 1-year cumulative incidence of recurrence was 31.3 % as shown in Table 2. 32.9 % of patients who did not recur eventually underwent elective surgery within the year. The time to recurrence ranged from 6 days to 4.8 months, with a median of 2 months. The vast majority of the patients with recurrences presented for a single recurrent visit

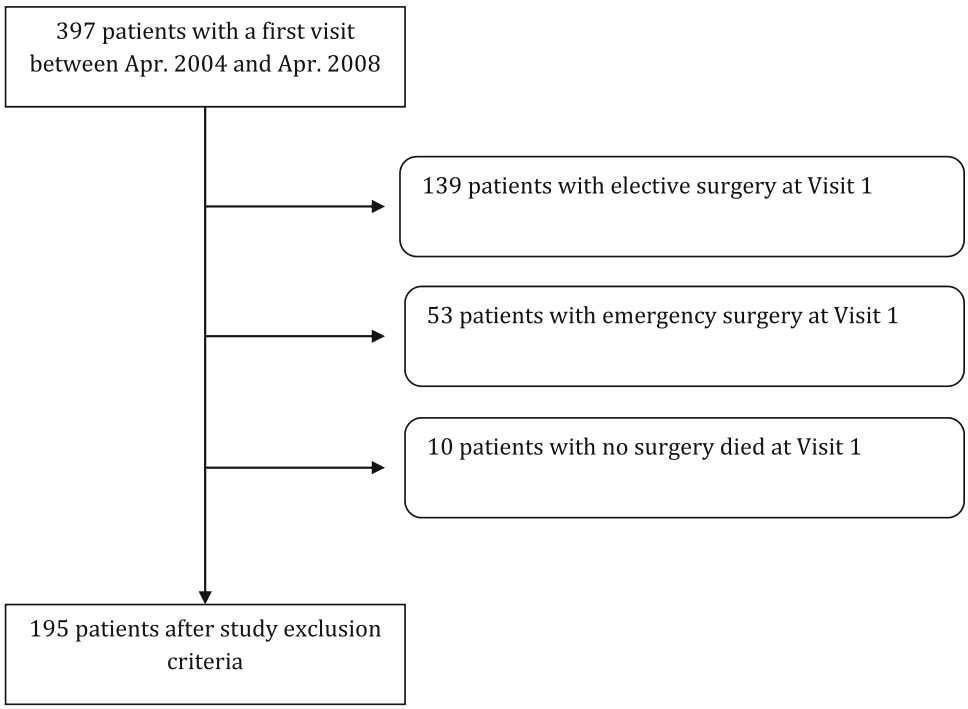

Fig. 1 Flow-chart for selection of target population

Table 1 Baseline demographics at first visit, overall and stratified by patients with and without recurrent visits

Characteristic	Recurrence ($n = 46$)	No recurrence ($n = 149$)	Overall ($n = 195$)
Age (mean ± SD)	77.4 ± 8.6	78.5 ± 7.6	78.3 ± 7.8
Gender (% male)	27 (58.7 %)	62 (41.6 %)	89 (45.6 %)
CCI (mean ± SD)	1.8 ± 1.8	2.2 ± 2.0	2.1 ± 1.9
ERCP or cholecystostomy tube	8 (17.4 %)	69 (46.3 %)	77 (39.5 %)
Diagnosis group			
Gallbladder disease	32 (69.6 %)	74 (49.7 %)	106 (54.4 %)
Common bile duct disease	14 (30.4 %)	75 (50.3 %)	89 (45.6 %)

CCI Charlson comorbidity index, *ERCP* endoscopic retrograde cholangiopancreatography

Table 2 Study outcomes over 1-year period

Among all patients	($n = 195$)
≥1 Recurrence	46 (31.3 %)
Among patients with no recurrence	($n = 149$)
Return visit for elective surgery	49 (32.9 %)
Among patients with ≥1 recurrence	($n = 46$)
Time to recurrence (months); median (range)	2.0 (0.2–4.8)
Number of recurrences	
1	37 (80.4 %)
2	8 (17.4 %)
3	1 (2.2 %)
Surgery	29 (63.0 %)
Emergency	20 (43.5 %)
Elective	9 (19.5 %)
Use of cholecystostomy tube	4 (8.7 %)
Use of ERCP	18 (39.1 %)
≥1 Complication (range 1–4)	16 (34.8 %)
Change in disease status from initial visit to first recurrent visit	
Gallbladder to CBD disease	8 (17.4 %)
CBD to gallbladder disease	2 (4.3 %)
No change	36 (78.3 %)

Data expressed as *n* (%) or median (inter-quartile range)

ERCP endoscopic retrograde cholangiopancreatography

Table 3 Survival analysis of time to recurrence ($N = 195$)

Effect	Hazard ratio	[95 % CI]	*p* value
Age	0.98	[0.94–1.02]	0.290
Males	1.80	[1.00–3.25]	0.050*
CCI	0.91	[0.77–1.08]	0.274
CBD versus GB disease	0.60	[0.32–1.14]	0.120
ERCP or tube at V1	0.30	[0.14–0.65]	0.002*

CI confidence interval, *GB* gallbladder, *CCI* Charlson comorbidity index

* Statistically significant

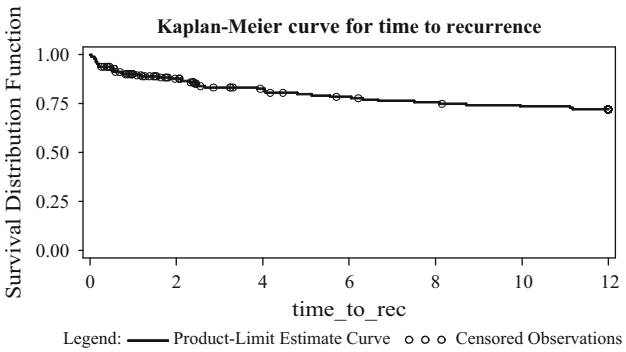

Fig. 2 Kaplan–Meier curves for time to recurrence

(80.4 %), while 17.4 % experienced two visits and only one patient returned for three visits. Among the 46 patients that recurred, 29 required surgery; 69 % of which was emergent, the remainder was performed in the elective setting (31 %). Complications occurred in 16 out of the 46 (34.8 %) patients who recurred; some experiencing up to four complications. In the recurrence group, 17.4 % of patients underwent a change in their disease status, from gallbladder disease to CBD disease. There were two mortalities in the patients who suffered a recurrence. One occurred after ERCP and the other after surgery. There was one mortality in a patient without a recurrence, who died of an unrelated cause.

In patients who did not undergo an intervention (ERCP or cholecystostomy) at V1, recurrence occurred in 32.2 % (38/118), whereas in those that did, recurrence was noted in 10.3 % (8/77). Table 3 summarizes the results of the survival analysis of time to recurrence, illustrated by the Kaplan–Meier curves in Fig. 2. Age and CCI were not found to be significant predictors of recurrence-free survival. Intervention (ERCP or cholecystostomy) at the first visit was found to be highly protective with an HR of 0.30 (95 % CI 0.14–0.65, $p = 0.002$). Males were 1.80-folds more at risk of recurrence when compared to females (1.00–3.25, $p = 0.050$). The nature of the biliary disease was not found to be a significant predictor of recurrent visits (0.60, 95 % CI 0.32–1.14, $p = 0.120$).

Discussion

The natural history of untreated gallstone disease has been well described. In 1960, Lund et al. [20] reported, in a landmark paper, a sub-group analysis of patients 65 years and older, who were symptomatic, but untreated, suffered a 50 % rate of severe symptoms or complications and a mortality of 7 %, in the 5 years following diagnosis. In the following two decades, large series and natural history studies, including the National Cooperative Gallstone Study, confirmed that in younger patients, once gallstones manifested themselves, symptomatic recurrence without surgical intervention was quite frequent, approaching 100 % over several years [21–23]. More recently, access to laparoscopy and ERCP has allowed surgeons to be more aggressive in treating gallstone disease, especially in older patients. Despite this, there still remains a significant number of patients who are treated non-operatively [14, 18, 24]. Because the selection criteria for non-operative management may have changed, there is a need to re-investigate the impact of this approach.

This is one of few studies focused on the issue of recurrence rates following non-operative management of biliary disease in elderly patients, in the era of minimally invasive surgical and endoscopic therapies. Our study shows that 31 % of elderly patients, who did not undergo a cholecystectomy at the time of their index presentation to the emergency room, subsequently developed recurrence of symptoms, with most of these recurrences occurring within the first 3 months. When looking exclusively at either acute cholecystitis or biliary pancreatitis in patients 65 years and older treated non-operatively at their initial admission, 2-year readmission rates were 27.3 [25] and 43 %, respectively [14]. These readmissions were associated with costs of up to $7,000 per readmission [25]. In younger patients, studies looking at the impact of treatment delays in biliary disease have reported similar numbers: a risk of recurrence of 13–30 %, with the majority of recurrences occurring in the first months [26–29]. In a population-based study, 10,304 patients did not undergo surgery on first admission for biliary disease and symptom recurrence was noted to be 14 % at 6 weeks, 19 % at 12 weeks, and 29 % at 1 year [30].

A prospective, randomised, multicentre trial studied patients aged 18–80 years after ERCP and sphincterotomy. They showed that a wait and see approach, over 2 years, was associated with 47 % symptom recurrence and 32 % morbidity. 81 % of patients eventually underwent cholecystectomy, but with a conversion rate of 55 % [31]. Other groups studying a younger patient population treated non-operatively, report complications rates of 20–30 % [27, 31, 32]. The high rate of complications in this study may be due to a very high proportion (43.5 %) of our patients with recurrences requiring emergency cholecystectomy, similar to what others have found in this age group [14]. While laparoscopic cholecystectomy in the elderly carries similar risks to the younger population when performed electively, emergency surgery carries a higher risk of conversion, morbidity, and mortality [12, 14, 33, 34]. Nevertheless, the 4 % mortality reported in this study, similar to the 3 % rate reported by Trust et al., compares favorably to higher reported rates in series of older patients: 16 % in patients 75 years and older [13], 9.5 % at 1 year in patients with a mean age of 80 [25], and 17.4 % at 1 year in patients with a median age of 85 [12].

In this study, 77 of the 195 patient study population underwent either ERCP or cholecystostomy tube at the initial visit. These interventions had a protective role, increasing the 1-year recurrence-free survival by 70 %. Female gender was also protective. The protective role of ERCP and gender has been established by others as well [14, 25, 35, 36]. Despite intervention, recurrence in this study was still 10 %. Short-term recurrence rates in elderly patients who undergo ERCP for acute biliary pancreatitis, without subsequent cholecystectomy, is 5–20 % [36–39]. Cholecystostomy tubes may be safe and effective in patients who are critically ill or who have medical comorbidities that preclude a surgical intervention [40, 41]; however, they may lower but do not eliminate recurrence. Recurrence rates after cholecystostomy for calculous disease in high-risk or elderly patients, when it is not followed by cholecystectomy, is 27–35 % and may be associated with significant morbidity [41–44].

Some important limitations of this study must be acknowledged. It was subject to the limitations inherent to chart reviews. We could not determine why certain patients underwent cholecystectomy, while others underwent non-operative management. The data may also give an incomplete picture of the trajectory of our study population, as they do not capture outpatient visits. Therefore, "first" visits or visits for recurrence represented manifestation of disease severe enough to warrant a hospital visit, so that we may be underestimating the true recurrence rate. Finally, patients may have also been seen in other hospitals, although inter-hospital movement is generally uncommon in this population.

Following non-operative management for symptomatic biliary disease, a third of elderly patients will, within 6 months, develop a recurrence severe enough to warrant a hospital visit. These recurrences are associated with significant rates of emergency surgery and morbidity. In selected patients, the use of percutaneous or endoscopic modalities may mitigate the risk of recurrence. Based on these data, we recommend that, regardless of age, unless medically contra-indicated, patients should undergo laparoscopic cholecystectomy at or soon after their index visit for biliary symptoms.

Disclosures Dr. Simon Bergman is a consultant for Baxter and Covidien. This relationship has not had an impact, nor constitute a conflict of interest with regards to this paper. Drs. Mohammed Al-Bader, Isabelle Vedel, Wael Hanna, Aaron Bilek, Christos Galatas, Jonah Marek, and Shannon Fraser have no conflicts of interest or financial ties to disclose. Nadia Sourial has no conflicts of interest or financial ties to disclose.

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